REMARKS

The Office Communication, mailed May 5, 2003, has been received and reviewed. Claims 7, 34, 35 and 38-40 are pending.

The applicants reply, mailed February 24, 2003, is not considered fully responsive to the prior Office Communication. The amended and newly submitted claims are alleged to be drawn to a non-elected invention.

Claims 7, 34, 35 and 38-40 have been canceled without prejudice or disclaimer. New claims 41-46 have been added. Basis for claims 41 to 46 can be found throughout the specification, for example, in paragraphs 28, 32, 48 and 78.

Claims 41-46 are currently pending and drawn to methods using two nucleic acid vectors for delivering a gene of interest. Claims 41-46 are newly added, therefore, the applicants have revised the response, mailed February 24, 2003, to reflect the new claim numbers and claim language. However, the current response is substantially the similar to the prior response.

Claims 41-46 are currently pending.

I. Drawings

Drawings were submitted February 24, 2003.

II. 35 U.S.C. § 112, first paragraph

Claims 7-9, 30 and 34-37 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement commensurate with the claim scope.

Independent claim 41 more definitely claims the present invention. Claims 41-46 recite the use of a recombinant adenovirus to deliver the gene of interest. Thus, the gene delivery vehicle is defined in the claims.

The Office alleges that delivering a gene of interest to any recipient cell is not enabled. Claims 41-46 do not recite "delivering a gene of interest to a recipient cell." Furthermore, as acknowledged by the Examiner on page 6 of paper 10, the adenoviral gene-therapy vector is effective in rats having antibodies directed to an adenovirus of the same serotype. Intratumoral injection was minimally affected and gene transfer to the liver and spleen was inhibited, but not

abolished. This example was designed to test the ability of immunization to protect the liver and spleen, not as an example of how to treat the liver or spleen. A person of ordinary skill in the art, using the guidance of the specification, would utilize an administration route consistent with the tissue to be treated.

The Office also alleges that a dose for a second vector that is greater than the neutralizing antibody is not enabled. The claims no longer recite the dose of the second vector, greater than an amount which can be neutralized by the humoral response. The Office alleges that Havey *et al.* teaches that humoral response to Ad vectors is affected by the route of administration, but not the dose. The applicants submit that Harvey *et al.* demonstrates a decreased humoral antibody response to Ad_{GV}CFTR.10 vector administered to the respiratory epithelium of cystic fibrosis patients. The authors themselves postulate that the decreased immune response may be an effect of the cystic fibrosis. Specifically, "the airway epithelium of these individuals is covered by high quantities of mucopurulent secretions which could preclude efficient Ad-vector infection of the airway epithelial cells." Harvey *et al.* at page 6737, col. 2, last paragraph. The authors acknowledge that the decreased humoral response may be due to a decrease in the effective administration of immunizing virus. Thus, Harvey *et al.* is inapplicable to a humoral response to adenovirus, wherein the adenovirus is specifically introduced to generate an immune response in humans.

Reconsideration and withdrawal of the rejection is respectfully requested.

III. 35 U.S.C. § 112, second paragraph

Claims 1-3, 5, 7-10, 13 and 27-37 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The claims were thought to be vague because the claims recite "essentially identical." Claims 1-40 have been canceled without prejudice or disclaimer. Claims 41-46 do not recite "essentially identical." Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 3, 27, 29 and 32 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being vague. These claims have been canceled without prejudice or disclaimer.

In regard to the rejection described in the first paragraph on page 10 of the Office

Communication, claims 41 to 46 more definitely recite that the antibodies are to be cross-reactive against the gene delivery vehicle. Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection.

IV. 35 U.S.C. § 102

Claims 1-3, 5, 7-10, 13, 27-30, 34 and 36 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bramson *et al.* Claims 1-40 have been canceled without prejudice or disclaimer.

Claim 41 now specifically recites "a human subject." Basis for the amendment can be found, for example, in paragraphs 22, 29 and 53.

Bramson *et al* does not anticipate claim 41, as each and every element of the claim is not taught by Bramson *et al.* Bramson *et al* disclose experiments in mice to determine if pre-existing anti-adenovirus antibodies (Ad-antibodies) would limit the effectiveness of subsequent gene therapy with adenovirus vectors. Because mice lack pre-existing Ad-antibodies, it was necessary to vaccinate the mice with a dose of adenovirus before the administration of the recombinant adenovirus gene-therapy vector. The results demonstrate that the recombinant adenovirus was still clinically effective despite the presence of Ad-antibodies in the treated mice.

The present invention provides the novel and inventive teaching that improves the administration of recombinant adenovirus to humans, by providing a human with a first adenovirus, which elicits antibodies reactive to the recombinant adenovirus gene-therapy vector, before the administration of said recombinant adenovirus. Bramson *et al* does not teach the person skilled in the art to actively provide humans with neutralizing adenovirus antibodies, because the experiments disclosed therein have been performed for a completely unrelated reason, and merely teaches that the inadvertedly present neutralizing Ad-antibodies in most humans do not prevent gene transfer into tumors (which is also described in the present specification, for example, in paragraphs 0023-0024). Thus, a person of ordinary skill in the art would not be motivated by Bramson *et al.* to actively induce the presence of neutralizing adenovirus antibodies in a human.

This conclusion is supported by the Office's position as stated on page 8 of the Office

Communication. Specifically, that it was known in the art that the host immunity to adenoviral vectors is a barrier for successful gene therapy and the art known strategy is to use an alternative serotype to circumvent the neutralizing antibodies. The instant specification provides a new concept that is contrary to the art known strategy. *Id.* Therefore, Bramson *et al.* does not anticipate the claims.

Furthermore, Bramson *et al.* observed that there appears to be less dissemination of the recombinant virus into peripheral organs when Ad-antibodies are present. This leads them to the suggestion that "**if organ toxicity is observed during the course of clinical trials**, it may be beneficial to immunize patients undergoing Ad-based therapies before the initiation of the clinical protocol" (page 1074, first column, line 3)(emphasis added). The invention is not limited to the instance where organ toxicity is observed during clinical trials: in fact, it teaches how to prevent such toxicity from the outset of the treatment, rather than act retrospectively when damage has already been done (see, for example, paragraph 0025 of the specification, described a tragic reason to start contemplating about possible improved adenovirus treatment regimes). Hence, the present invention claims providing the subject with a first adenovirus and raising antibodies directed to an adenovirus of the same serotype as the recombinant adenovirus containing the gene of interest in each and every instance where treatment with a recombinant adenovirus is done, *i.e.* irrespective of the presence or absence of other indicators. This means that all humans amenable to treatment with recombinant adenovirus could be treated according to the method of the invention.

Therefore, the applicants respectfully submit that the claims, as amended, are not anticipated by Bramson *et al.* Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 2, 5, 10, 13, and 28 have been canceled without prejudice or disclaimer. Thus, the rejections over Song *et al* and Russi *et al* are considered moot.

V. 35 U.S.C. § 103

Claims 1, 2, 5, 31 and 33 stand rejected under 35 U.S.C. § 103 as being unpatentable over Russi *et al.* in view of Esandi *et al.* Claims 1, 3 and 32 stand rejected under 35 U.S.C. § 103 as

being unpatentable over Bramson *et al.* in view of Esandi *et al.*

Claims 1-3, 5, 31 and 32 have been canceled without prejudice or disclaimer. Thus, the rejections over Russi *et al.* in view of Esandi *et al.* and Bramson *et al.* in view of Esandi *et al.* are considered moot.

CONCLUSION

In the event questions remain after consideration of these remarks and amendments, the Office is kindly requested to contact applicant's attorney at the number given below.

Respectfully submitted,

G. Scott Dorland, Ph.D.
Registration No. 51,622
Attorney for Applicant(s)
TRASKBRITT
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

Date: May 23, 2003
GSD/gsd
Document in ProLaw